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Short Communication

Additive effect of oxitropium bromide in combination with inhaled corticosteroids in the treatment of elderly patients with chronic asthma

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Abstract

The efficacy of the addition of inhaled oxitropium bromide in combination with inhaled corticosteroids in the treatment of elderly asthmatic patients whose asthma is not well controlled was evaluated. A randomized, open-label cross-over trial comparing 4-week treatment periods with and without regular inhalation of 200 μg of oxitropium bromide four times per day was performed. Twenty-four patients (mean age ± SD: 62 ± 7 years) completed the study. The dose of beclomethasone dipropionate in this patient group was 1300 ± 800 μg/day. Forced expiratory volume in 1 second (FEV_1) was significantly improved after treatment with regular inhalation of oxitropium bromide when compared with FEV_1 after treatment without oxitropium (1.73 ± 0.60 *vs* 1.63 ± 0.68). Both morning and evening peak expiratory flow rates were significantly greater during the treatment period with regular inhalation of oxitropium bromide. The score for dyspnea/chest tightness was also significantly improved during the oxitropium bromide period. There was no statistically significant improvement in forced vital capacity, scores for other symptoms or the frequency of rescue inhalation of fenoterol. The results of this study demonstrated that the addition of regular inhalation of oxitropium bromide is beneficial in elderly asthmatics whose asthma is not well controlled, even when treated with high-dose inhaled steroids.

Key words: beclomethasone dipropionate, bronchial asthma, dyspnea, inhaled corticosteroids, oxitropium bromide, peak expiratory flow.

Introduction

Although inhaled corticosteroids are the established treatment of choice in cases of chronic asthma, it is not uncommon for even high doses of inhaled corticosteroids to fail in achieving optimal control of asthma.[1] The addition of other bronchodilators including sustained-release theophylline and/or inhaled anticholinergic agents has been recommended in the treatment of patients whose asthma is not well controlled with inhaled corticosteroids.[1] Inhaled anticholinergic agents administered by single-dose inhalation have been shown to be effective in terms of acute bronchodilation in patients with asthma.[2–5] The long-term efficacy of drugs of this class, however, remains to be adequately documented.

Inhaled anticholinergic agents have been regarded as the drug of choice for patients with chronic obstructive pulmonary disease (COPD)[6] due to the lower incidence of systemic side-effects. It has been suggested that they have a greater bronchodilating effect than β_2-receptor agonists in elderly asthmatic patients.[7] In order to evaluate the efficacy of the addition of inhaled oxitropium bromide in elderly asthmatic patients using

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inhaled corticosteroids and whose asthma was not well controlled, we performed a randomized, open-label cross-over trial.

METHODS

Subjects

Patients with chronic asthma aged 50 years or over who had been suffering asthmatic symptoms and who had a peak expiratory flow rate (PEF) of less than 85% of the individual best value for 2 weeks were recruited. In total, there were twenty-four patients (14 male and 10 female) with ages ranging from 52 to 76 years (mean age ± SD: 62 ± 7 years). All of the patients had received treatment with a constant dose (400 μg/day or more) of beclomethasone dipropionate (BDP) for at least 2 weeks. The diagnosis of asthma was based on the definition provided by the the British Thoracic Society.[1] For each patient it was also confirmed that the improvement of PEF to inhaled β_2-receptor agonists was more than 15%. Patients with COPD or those taking other anti-asthma medications apart from β_2-receptor agonists were excluded. Those patients whose PEF recording was in doubt or whose compliance with the inhalation technique was questionable were also excluded. Informed consent was obtained from all participants.

Study protocol

The efficacy of treatment with and without regular inhalation of oxitropium bromide in addition to inhaled BDP was compared using a randomized, open-labeled cross-over trial. After a run-in period of at least 2 weeks' duration, two continuous treatment periods of 4 weeks' duration each were used. A total of 200 μg of oxitropium bromide was administered four times per day by a metered dose inhaler during the treatment period.

Education regarding inhalation technique, recording of PEF and symptom scores was provided at least 2 weeks prior to entry into the study and compliance was confirmed to be satisfactory by an attending physician during the run-in period. The dose of BDP was kept at the same level from 2 weeks before the entry to the end of the study. Two puffs of fenoterol (400 μg) were prescribed on an as-needed basis but no other medications were allowed.

Outcome measures

Outcome measurements included daily recording of morning and evening PEF, symptom scores and frequency of rescue inhalation of fenoterol during the last two weeks of each 4-week treatment period as well as spirometry performed at hospital visits before entry and at the end of each treatment period. The baseline PEF and symptom scores were recorded over the 2-week period just before entry into the study.

The PEF was recorded twice daily before inhalation of BDP with or without oxitropium bromide. A Personal Best Peak Flow Meter™ (Health Scan, Cedar Grove, NJ, USA) was used for ambulatory PEF measurement and a maximum of three measurements was recorded. Three subjective symptoms were recorded daily using a scoring system ranging from 0 to 4 points (0 = never, 4 = severe): dyspnea/chest tightness, coughing and sputum. The frequency of the rescue inhalation using fenoterol was also recorded.

The predicted values for the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were those established by the Japan Society of Chest Diseases.[8] Peak expiratory flow was expressed as a percentage of the individual best value.

Statistical analysis

The paired *t*-test was performed for the analysis of FEV_1, FVC and PEF. The Wilcoxon signed-rank test was used for the evaluation of symptom scores and the frequency of rescue inhalation of fenoterol. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

All 24 patients who participated completed the study. The baseline FEV_1 for patients was 1.60 ± 0.60 L or 60 ± 2% of the predicted values. The dose of BDP in this patient group was 1300 ± 800 μg/day (range: 400–2400 μg/day). In 12 patients oxitropium bromide was administered during the first treatment period, followed by the period without oxitropium bromide. The other 12 patients received oxitropium bromide in the second period.

FEV_1 was significantly improved after treatment with regular inhalation of oxitropium bromide when compared with the measurements taken after treatment without oxitropium (Table 1). Both morning and evening PEF values were significantly better during the treatment period with regular inhalation of oxitropium bromide than during the period without oxitropium. The score for dyspnea/chest tightness was also significantly improved during the oxitropium bromide period. Scores for other symptoms

Table 1. The additive effect of oxitropium bromide combined with beclomethasone dipropionate

	Baseline	With OB	Without OB	*P**
FEV_1 (L)	1.61 ± 0.58	1.73 ± 0.60	1.63 ± 0.68	< 0.05
% predicted	60.5 ± 22.0	66.8 ± 22.2	62.0 ± 23.8	< 0.05
FVC (L)	2.61 ± 0.70	2.72 ± 0.63	2.61 ± 0.72	NS
% predicted	75.7 ± 15.5	81.6 ± 16.0	77.0 ± 16.3	NS
Morning PEF (L/min)	310 ± 70	320 ± 70	290 ± 67	< 0.001
% best	70 ± 9	74 ± 12	67 ± 11	< 0.001
Evening PEF (L/min)	330 ± 70	330 ± 80	310 ± 70	< 0.01
% best	73 ± 11	78 ± 13	72 ± 12	< 0.01
Weekly symptom scores				
Dyspnea/Chest tightness (0–28)	11 ± 13	6 ± 13	10 ± 16	< 0.01
Cough (0–28)	17 ± 16	13 ± 18	15 ± 21	NS
Sputum (0–28)	22 ± 16	20 ± 19	21 ± 21	NS
Total symptom (0–84)	49 ± 34	38 ± 40	45 ± 50	NS
Frequency of rescue fenoterol inhalation (per week)	6.0 ± 5.4	3.9 ± 5.4	4.4 ± 5.4	NS

OB, oxitropium bromide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; % best, percentage of the individual best peak expiratory flow; NS, not significant; *, comparisons were made between two treatment periods. Values are expressed as mean ± SD.

were not significantly different between the two treatment periods nor was the frequency of rescue fenoterol inhalation. No order effects or carry-over effects were found between the oxitropium-first and the oxitropium-second regimens in the measurements of lung functions and symptom scores.

No adverse side-effects were reported during the entire study period.

Discussion

The mean age of patients in this study was 62 years and on average patients took 1300 μg of BDP. This indicated that elderly patients whose asthma was not adequately controlled even with high doses of BDP were investigated in this study. The results of this study show the beneficial effect of the addition of inhaled oxitropium bromide to BDP on the study population. In this patient group oxitropium bromide was shown to be effective in improving FEV_1, PEF and the score for dyspnea/chest tightness. Anticholinergic agents such as ipratropium bromide or oxitropium bromide have been reported to have a significant bronchodilating effect in asthmatic patients when evaluated by single-dose acute bronchodilator response tests.[2–5] The addition of oxitropium bromide to BDP, as shown in this study, was also associated with improvements of PEF and FEV_1, suggesting that the bronchodilating effect of this drug was maintained over the 4-week period and contributed to improved control of chronic asthma.

The British Thoracic Society recommends a sequential therapeutic trial of one or more of the following products as a step 4 treatment where asthma cannot be adequately controlled with 800–2000 μg/day of BDP: inhaled long-acting β_2-agonists, sustained-release theophylline, inhaled ipratropium or oxitropium, long-acting β_2-agonist tablets, high dose inhaled bronchodilators, or cromoglycate or nedocromil.[1] Among these supplementary treatments, inhaled long-acting β_2-receptor agonists[9] and sustained-release theophylline[10] have been shown to have an additive effect when combined with high doses of BDP in patients with asthma. However, to date the efficacy of oxitropium bromide in this regard has not been studied. This report is the first to show the effect of adding oxitropium bromide to BDP and confirms the validity of one of the recommendations of the British Thoracic Society.

Although significant improvement was observed in the present study, the magnitude of the improvement appears to be rather small. Patients whose asthma is not adequately treated even with high doses of BDP are not uncommon and a comparison of the additive effects and safety of various bronchodilating drugs including sustained-release theophylline, long-acting β_2-receptor agonists and anticholinergic agents is needed in patients with asthma.

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